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| EXAMINER | |
|---|---|
| REDDIG, PETER J | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/775,481 | WALDMAN ET AL. | |
| | Examiner | Art Unit | |
| | PETER J. REDDIG | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *64,65,68-70,72,74,75,91-103,132,145,147,148 and 150-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,65,68-70,72,74,75,91-103,132,145,147,148 and 150-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2009 has been entered. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are currently under consideration as drawn to the previously elected species of 5-fluorouracil and bleomycin. It is noted that the election of species of cancers and guanylyl cyclase C ligand, and route of administration have been rejoined for examination.

### *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof *conjugated to a therapeutic agent* for at least six

hours; and b) subsequently administering a different therapeutic agent, *does not* reasonably provide enablement for a method of inducing a cytostatic effect in a primary or metastasized colorectal, gastric, or esophageal cancer cell in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the step of: administering by infusion into the circulatory system of said individual, a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and induce a cytostatic effect in said cells, a method of inhibiting the proliferation of a primary or metastasized colorectal, gastric, or esophageal cancer cell in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the step of: administering into the circulatory system of said individual a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and inhibit proliferation of said cells, a method of killing primary or metastasized colorectal, gastric, or esophageal cancer cells in an individual who has been identified as having

primary or metastasized colorectal, gastric, or esophageal, said method comprising the steps in the following order: a) administering to said individual a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand, wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and inhibit proliferation of said cells and wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration ≥EC50 of said guanylyl cyclase C ligand and b) subsequently administering a different therapeutic agent, or a method of killing primary or metastasized colorectal, gastric, or esophageal, cancer cells in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof for at least 6 hours; and b) subsequently administering a different therapeutic agent. . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the

amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to:

64. A method of inducing a cytostatic effect in a primary or metastasized colorectal, gastric, or esophageal cancer cell in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the step of: administering by infusion into the circulatory system of said individual, a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and induce a cytostatic effect in said cells.

65. A method of inhibiting the proliferation of a primary or metastasized colorectal, gastric, or esophageal cancer cell in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the step of: administering into the circulatory system of said individual a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl

cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and inhibit proliferation of said cells.

169. A method of killing primary or metastasized colorectal, gastric, or esophageal cancer cells in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the steps in the following order: a) administering to said individual a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation h by the cytostatic effect of the guanylyl cyclase C ligand, wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric, or esophageal cancer cell in said individual and inhibit proliferation of said cells and wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration $\geq$EC50 of said guanylyl cyclase C ligand and b) subsequently administering a different therapeutic agent.

170. A method of killing primary or metastasized colorectal, gastric, or esophageal cancer cells in an individual who has been identified as having primary or metastasized colorectal, gastric, or esophageal cancer, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof for at least 6 hours; and b) subsequently administering a different therapeutic agent.

The specification teaches that ligands for guanylyl cyclase C are compounds that specifically bind to the receptor and include guanylin and uroguanylin, may be a peptide or a non-peptide, and the ligands may be conjugated or unconjugated, see p. 15-lines 3-12. Thus the claims encompass using any of these ligands in an unconjugated, cytostatically effective amount

sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days or at least 30 days.

The specification teaches that heat-stable toxin (ST), which is a peptide produced by E. *coli,* can inhibit cell proliferation of cultured guanylyl cyclase C expressing T84 colon carcinoma cells in a CNG calcium channel dependent manner, see p. 53-59 and Figs. 1-4. The specification teaches that ST inhibited in colorectal cancer cells the release of matrix metalloproteinase 9, the organization of the actin cytoskeleton, and increased the adherence of colorectal cancer cells to type IV collagen, which are changes that could potentially inhibit the metastatic phenotype of colorectal cancer cells, see p. 63 and 64.

One cannot extrapolate the teachings of the specification to the enablement of the scope of the claims because no nexus has been established between the unconjugated ligands to guanylyl cyclase C and inducing a cytostatic effect or killing in primary or metastasized colorectal, gastric, or esophageal cancer cells by an amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 or at least 30 days or an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand. Furthermore, the specification has not shown what treatment protocol will maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days or at least 30 days or an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand.

Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited) teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1. US Patent No. 5,879,656

(previously cited) teaches treating metastasized colorectal cancer with the guanylyl cyclase C ligand uroguanylin (SEQ ID NO: 5) and related GCC ligands conjugated to therapeutic agents, see the claims. However, other than uroguanylin, the art does not teach that unconjugated GCC ligands can treat primary or metastasized colorectal cancer and the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable. In particular, Gura (Science, 1997, 278:1041-1042, previously cited) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 2004/0180002, September 15, 2004, previously cited) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the

published application). Additionally, the ability to generate an antibody to a GCC receptor does not predictably mean that the antibody will have a cytostatic or cell killing effect on cells expressing GCC receptors. In particular, Young et al. (US Patent Application Pub. 2004/0197328, October 7, 2004) teach that even for monoclonal antibodies that recognize the same protein, it cannot be predicted if the antibody will be of therapeutic benefit. In particular, Young et al. teach that while monoclonal antibody 11BD-2E11-2, which recognizes Melanoma-associated chondroitin sulfate proteoglycan (MCSP), is effective for treatment of breast and ovarian tumors (see examples 7 and 8), other monoclonal antibodies that also recognize MCSP, such as 9.2.27 and 225.28S, were ineffective as therapeutic antibodies, see para. 0014-0019. Additionally, Young et al. (US Pat. App. Pub 2004/0258693, Dec. 23, 2004) teaches that although monoclonal antibody 7BD-33-11A binds to multiple cell lines, it only induced cytotoxicity in a small subset of those cells to which it bound, see Table 1 and 2 and para. 0100-0102. Thus, binding of antibody to its target protein is not predictably indicative of its activity towards a cell expressing the protein. Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the broadly claimed un-conjugated guanylyl cyclase C ligands would predictably be useful for inducing a cytostatic effect in primary or metastasized colorectal, gastric, or esophageal cancer cells in an individual, inhibiting proliferation of primary or metastasized colorectal gastric, or esophageal cancer cells in an individual, or to kill primary or metastasized colorectal, gastric, or esophageal cancer cells in an individual.

Furthermore one of skill in the art would not predictably be able to maintain a concentration ≥EC50 of the broadly claimed guanylyl cyclase C ligands for at least 15 days or at least 30 days or in an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand as insufficient guidance and direction has been provided as to what dose protocol would maintain a concentration ≥EC50 of the broadly claimed guanylyl cyclase C ligands for the indicated times at the indicated levels or that these concentrations would be effective for inducing a cytostatic effect on, inhibit proliferation of, or kill primary or metastasized colorectal cancer cell . The broadly claimed guanylyl cyclase C ligands may be degraded *in vivo* before achieving the claimed concentrations by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the GCC ligands may be absorbed by fluids, cells and tissues and, circulation into the target area may be insufficient to maintain the claimed concentrations of the broadly claimed guanylyl cyclase C ligands. In particular, Wolfe et al. (The J. of Nuclear Medicine March 2002, 43: 392-399) teach that a GCC ligand, NC100586, has rapid clearance from the blood by urinary excretion. See p. 395, Tables 1 and 2, and Fig.1. Given that the pharmacokinetics have not been described for the broadly contemplated and claimed GCC ligand and given the rapid clearance of the GCC ligands after intravenous administration, one of skill in the art one of skill in the art would not predictably be able to maintain a concentration ≥EC50 of the broadly claimed guanylyl cyclase C ligands for at least 15 days or at least 30 days or in an amount sufficient to maintain a concentration greater than or equal to 10 times the EC50 of the GCC ligand without undue experimentation. Furthermore, even if one were able to maintain the claimed concentration of GCC ligands in the circulatory system these levels of GCC ligand may be not be tolerable in a

patient. In particular, Carrithers et al. (Kidney Int. 2004 65: 40-53) teach intravenous administration of guanylin, uroguanylin, and E. coli heat stable enterotoxins, all GCC ligands, case significant natriuresis (excretion of sodium in the urine), kaliuresis (excretion of potassium in the urine), and diuresis (increased excretion of urine). See Abstract and Table 5. Additionally, Carrithers et al. teach that sodium excretion by the kidney needs to be precisely regulated, with changes in sodium levels potentially being life threatening. See p.51-2nd col. and also Dorland's Medical Dictionary for Healthcare Consumers (salt-losing crisis/salt-losing syndrome, Elsevier, http://www.mercksource.com/pp/us/cns/cns_home.jsp, 2007). Thus, one could not predictably use the GCC ligands at the claim levels without further guidance and direction as to this treatment method's effect on kidney function and sodium homeostasis. Given the above, in the absence of *in vivo* experimental data demonstrating a protocol would maintain a concentration ≥EC50 of the broadly claimed guanylyl cyclase C ligands for at least 15 or 30 days or maintain a concentration of greater than or equal to 10 times the EC50 of the guanylyl cyclase C ligand or that this concentration would be effective for inducing a cytostatic effect on, inhibit proliferation of, or kill primary or metastasized colorectal, gastric, or esophageal cancer cells, one of skill in the art could not predict that the invention will function as claimed with a reasonable expectation of success .

Furthermore, no evidence has been presented in vitro or in vivo that unconjugated GCC ligands or anti-GCC antibodies have any effect on the growth or survival of gastric or esophageal cancer cells or that gastric or esophageal cells express GCC receptors and it is well known in the art that cancers are heterogeneous in their phenotypes and responses to therapeutic agents. In particular, cancers comprise a broad group of malignant neoplasms divided into two categories,

carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected that cancers that originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between GCC ligands and colorectal cancer, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al. (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore, Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of

cancer, see Carter, S. K. et al. (Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C). Given the above, it is clear that it is not possible to predictably extrapolate any correlation between GCC ligands and colorectal cancer and sensitivity to GCC ligands in gastric or esophageal cancer, based on the information in the specification and known in the art without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

Applicants argue that the presently claimed invention is enabled because one of skill in the art would not need to be use undue experimentation to practice the claimed invention. The Office alleges that "other than uroguanylin, the art does not teach that unconjugated GCC ligands can treat primary or metastasized colorectal cancer and the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable." (Office Action, page 8). The Office cites Gura (Science, 1997, 278:1041-1042) as evidence of the unpredictability. The Office, however, has not provided any reasonable evidence to question the enablement of the presently claimed invention, there is nothing in the references cited by the Office that supports a reasonable basis to question the enablement of the presently claimed invention.

Applicants argue that as the M.P.E.P. explains, "in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement

provided for the claimed invention. (M.P.E.P. § 2164.04, citing In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)) "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.'" In re Marzocchi 439 F.2d at 224, 169 USPQ at 370 (CCPA 1971). The Examiner has not put forward any evidence other than evidence that certain compounds may not gain FDA marketing approval. This standard, however, is not the standard for patentability.

Applicants argue that the presently claimed invention is directed to various methods. The cited references demonstrate the methods, such as those presently claims, are not unpredictable to the point where undue experimentation would be required. Whether the presently claimed methods are sufficient to gain FDA marketing approval is an unrelated and separate issue. The Office's citation of Young et al. (U.S. Patent Application No. 2004/0180002) does not support the Office's rejection. In contrast, Young supports that conclusion that the presently claimed invention is enabled. Young describes an antibody that can halt tumor progression. Young also refers to clinical trial data where success in at least one patient was also shown. These results do not show that the methods are not enabled, but rather that one of skill in the art would understand that nothing more than following the specification and, at most, routine experimentation would be required to practice the presently claimed methods. Predictability of FDA approval for marketing a therapeutic is not required to satisfy the enablement requirement.

Applicants' arguments have been considered, but have not been found persuasive because the Examiner has not argued that the claimed method must meet a FDA level of approval to be

enabled. For the reasons set forth above the methods as broadly claimed could not be predictably be made and use given the unpredictability in the art set forth above. Although Young shows one antibody that can halt tumor progression, the identification of such antibodies is unpredictable for the reasons set forth above. Given the above and given that neither the specification nor art of record teaches anti-GCC antibodies or the broadly claimed GCC ligand that can function to kill or induce a cytostatic effect in colorectal, gastric, or esophageal cancer cells when used in the claimed methods, undue experimentation would be required to use the method as broadly claimed without undue experimentation.

Applicants argue that the Office also alleges that it would not have been predicable to maintain a concentration as recited in the claims. The Office provides no evidence other than generalized conclusions that the ligands "may be degraded in vivo before achieving the claimed concentrations." The Office also states that "it **appears** that undue experimentation would be required to practice the claimed invention." (emphasis added, Office Action, page 10). The standard used by the Office is not sufficient to shift the burden. A claim cannot just "appear" to require undue experimentation, rather a claim is not enabled if undue experimentation would be required. Thus, the Office's standard in concluding that the claims are not enabled is incorrect. The Office also fails to support the enablement rejection with any evidence. As discussed above, the Office must establish that there is a reasonable basis to question the enablement. Here, the Office has not established a reasonable basis because the allegations are unsubstantiated. If the rejection is maintained Applicants respectfully request that the Office submit an affidavit attesting to the facts used to conclude that the claims are not enabled.

Applicants' argue that in contrast to the Office's rejection, the specification provides how to administer the ligand and at what concentrations. One of skill in the art can follow the specification without having to perform undue experimentation. None of the references cited by the Office contradict the present specification and none of the references establish a reasonable basis to question the enablement of the present claimed invention. Accordingly, the claims are enabled.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have not provided any evidence that the recited doses will maintain the broadly claimed GCC ligands at the levels and times claimed. Thus, given that the GCC ligands are rapidly cleared from the circulation, as set forth above, in absence of further guidance or exemplification one of skill in the art could not predictably use the method as broadly claimed without undue experimentation. Additionally, the use of the word "appears" does not alter the fact that the factors for undue experimentation set forth in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988), which do not required an affidavit on the part of the Office, were used to determine whether undue experimentation was required making the using the method as broadly claimed. Thus, weighing all of the factual considerations, undue experimentation would be required to make and use the method as broadly claimed for the reasons set forth above.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3.. Claims 169-174 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,879,656 (March, 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8, previously) and in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

It is note that the broadest reasonable interpretation of claims 169-174 includes antibodies conjugated to a therapeutic agent. US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibodies conjugated therapeutic agents to individuals for therapy of primary or

metastasized colorectal cancer, see claims 30 -31, col. 10-lines 33-45. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously, see col. 17-lines 25-33. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65. Thus, given that US Patent No. 5,879,656 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

US Patent No. 5,879,656 teaches as set forth above, but does not teach maintaining a plasma concentration $\geq$ EC50 or a concentration greater than or equal to 10 times the EC50 of the antibody conjugates, administering it for at least 6 hours, or humanized anti-guanylyl cyclase C monoclonal antibody.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to maintain a plasma concentration ≥ EC50 or a concentration ≥to 10 times the EC50 of the anti-GCC antibody conjugates or administer the antibodies for at least 6 hours, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to modify the teachings of US Patent No. 5,879,656 to maintain a plasma concentration ≥ EC50 of the anti-GCC or a concentration ≥to 10 times the EC50 antibody conjugates or administer the antibodies in order to optimize the dose needed to treat a tumor and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Queen et al teach a reproducible technique for making humanized monoclonal antibodies (page 11030, col. 2 para 3) and further teaches that for human applications humanized monoclonal antibodies are more useful because of their reduced immunogenicity (page 10029, col. 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the

six hypervariable regions from the heavy- and light-chain domains of a rat (monoclonal) antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to and one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 5,879,656 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized monoclonal antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse monoclonal antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Applicants argue that claim 173 depends from claim 170, which has been amended. The cited references alone or in combination do not yield the presently claimed invention.

Accordingly, claim 173 is not obvious.

Applicants' arguments have been considered, but have not been found persuasive because it would have been obvious to modify the concentration and time to find the doses most suitable for treatment for the reasons set forth above.

4. Claims 169-174 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,767,704 (Waldman March 27, 2000, previously cited), in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

It is note that the broadest reasonable interpretation of claims 169-174 includes antibodies conjugated to a therapeutic agent. US Patent No. 6,767,704 teaches administering anti-guanylyl cyclase C humanized monoclonal antibodies conjugated therapeutics to individuals for therapy of primary or metastasized colorectal cancer, see claims col. 3-lines 50-55, col. 21-lines 55-60, col. 22-line 55 to col. 23-line 67, and col. 31-lines 63-67. US Patent No. 6,767,704 teaches that the compositions of the invention can be used to kill the cancer cells, see col. 21-lines 45-55. US Patent No. 6,767,704 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously, see col. 26-lines 4-11. US Patent No. 6,767,704 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see col. 22-line 55 to col. 23-line 67. Thus, given that US Patent No. 6,767,704 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would

immediately envision administering the antibody and different therapeutic agents in the claimed order.

US Patent No. 6,767,704 teaches as set forth above, but does not teach maintaining a plasma concentration ≥ EC50 or a concentration ≥to 10 times the EC50 of the antibody conjugates, or administering it for at least 6 hours.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to maintain a plasma concentration ≥ EC50 or a concentration ≥to 10 times the EC50 of the anti-GCC antibody conjugates or administer the antibodies for at least 6 hours because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to modify the teachings of US Patent No. 5,879,656 to maintain a plasma concentration ≥ EC50 or a concentration ≥to 10 times the EC50 of the anti-GCC antibody conjugates or administer the antibodies in order to optimize the dose needed to treat a tumor and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the

general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-32, 35-38, 40-55, and 57-65 of copending Application No. 10/866,951 in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8, previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with esophageal cancer comprising administering a GCC ligand and active agent, wherein the ligand is an antibody or monoclonal antibody and is conjugated to the agent, wherein the agent is a chemotherapeutic, toxin, or radiosensitizing agent, wherein the agent inhibits cell division, wherein the agent is bleomycin or 5-FU,.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time (abstract).

Queen et al teach a reproducible technique for making humanized monoclonal antibodies (page 11030, col. 2 para 3) and further teaches that for human applications humanized monoclonal antibodies are more useful because of their reduced immunogenicity (page 10029, col 2, para 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat (monoclonal) antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for

use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to maintain a plasma concentration ≥ EC50 conjugates or a concentration ≥ to 10 times the EC50 of the anti-GCC antibody or administer the antibodies for at least 6 hours of the conjugated GCC antibody or therapeutic agents taught by 10/866,951, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to maintain a plasma concentration ≥ EC50 or a concentration ≥to 10 times the EC50 of the anti-GCC antibody conjugates or administer the antibodies for at least 6 hours and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized forms of the monoclonal antibodies of 10/866,951with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that in view of the amendment to claim 170, which recites that the antibody is administered for at least 6 hours the obviousness-type double patenting rejections have been obviated. Accordingly, the presently claimed invention is not obvious and, thus, not subject to an obviousness-type double patenting rejection.

Applicants' arguments have been considered, but have not been found persuasive because it would have been obvious to modify the concentration and time to find the doses most suitable for treatment for the reasons set forth above.

6. Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 9, 10, 15-18, 23, 28-35, 38-43 46-50, and 53-58 of US Patent 5,879,656, (March, 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the Patent and the instant application are claiming common subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with metastasized colorectal cancer comprising administering guanylyl cyclase C (ST receptor) binding moiety and active moiety, wherein the binding moiety is an antibody or binding fragment thereof and is conjugated to the active moiety, wherein the active moiety is a chemotherapeutic, toxin, or radiosensitizing agent, bleomycin or 5-FU.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use to maintain a plasma concentration $\geq$ EC50 conjugates or a concentration $\geq$to 10 times the EC50 of the anti-GCC antibody or administer the antibodies for at least 6 hours of the conjugated GCC antibody or therapeutic agents taught by US Patent 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration, dose and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 5,879,656 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Applicants argue that in view of the amendment to claim 170, which recites that the antibody is administered for at least 6 hours the obviousness-type double patenting rejections have been obviated. Accordingly, the presently claimed invention is not obvious and, thus, not subject to an obviousness-type double patenting rejection.

Applicants' arguments have been considered, but have not been found persuasive because it would have been obvious to modify the concentration and time to find the doses most suitable for treatment for the reasons set forth above.

7. Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8 of US Patent 6,060,037

in view of US Patent 5,879,656, (March 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Claims 6-8 of US Patent 6,060,037 are drawn to a method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual a therapeutically effective amount of a sterile pharmaceutical composition that comprises a) a pharmaceutically acceptable carrier or diluents, and, b) a conjugated compound which comprises i) a ST receptor binding moiety; and, ii) an active moiety that is a therapeutic agent that causes cell death; wherein said conjugated compound binds to an ST receptor on a metastasized colorectal tumor cell and said active moiety causes the death of said cell and, wherein said pharmaceutical composition is administered for delivery into said individuals circulatory system.. A method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual for delivery into said individual's circulatory system a therapeutically effective amount of a pharmaceutical composition comprising: a) a pharmaceutically acceptable carrier or diluents, and, b) an amount of conjugated compound effective for therapeutic use in a human suffering from colorectal cancer, said conjugated compound comprising: i) an ST receptor binding moiety; and, ii) an active moiety; wherein said pharmaceutical composition is sterile and said active moiety is a radioactive agent; wherein said conjugated compound binds to ST receptors on a metastasized colorectal cancer cell and accumulates on said cell, and radiation emitted from accumulated conjugated compound on said cell causes the death of said cell.

US Patent 6,060,037 contemplates antibodies as a receptor binding moiety, see col. 11, lines 1-7.

US Patent 5,879,656 teaches as set forth above.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use to maintain a plasma concentration ≥ EC50 conjugates or a concentration ≥to 10 times the EC50 of the anti-GCC antibody or administer the antibodies for at least 6 hours of the conjugated GCC antibody of the conjugated GCC antibody or therapeutic agents taught by US Patents 6,060,037 and 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration, concentrations and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 6,060,037 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Applicants argue that in view of the amendment to claim 170, which recites that the antibody is administered for at least 6 hours the obviousness-type double patenting rejections have been obviated. Accordingly, the presently claimed invention is not obvious and, thus, not subject to an obviousness-type double patenting rejection.

Applicants' arguments have been considered, but have not been found persuasive because it would have been obvious to modify the concentration and time to find the doses most suitable for treatment for the reasons set forth above.

8. Claims 169-174 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-16 US Patent 6,087,109 (July, 2000), in view of US Patent 5,879,656, (March 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Claims 14-16 of US Patent 6,087,109 are drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising the steps of administering to said individual a therapeutically effective amount of a pharmaceutical composition comprising a conjugated compound comprising: a) a ST receptor binding moiety; and, b) an active moiety; wherein said active moiety is an antisense molecule, wherein said pharmaceutical composition is administered orally, or wherein said pharmaceutical composition is administered intravenously.

US Patent 6,087,109 contemplates antibodies as a receptor binding moiety, see col. 9, lines 25-33.

US Patent 5,879,656 teaches as set forth above.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use to maintain a plasma concentration $\geq$ EC50 conjugates or a concentration $\geq$ to 10 times the EC50 of the anti-GCC antibody or administer the antibodies for at least 6 hours of the conjugated GCC antibody or therapeutic agents taught by US Patents 6,087,109 and 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration, concentrations, and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 6,087,109 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Applicants argue that in view of the amendment to claim 170, which recites that the antibody is administered for at least 6 hours the obviousness-type double patenting rejections have been obviated. Accordingly, the presently claimed invention is not obvious and, thus, not subject to an obviousness-type double patenting rejection.

Applicants' arguments have been considered, but have not been found persuasive because it would have been obvious to modify the concentration and time to find the doses most suitable for treatment for the reasons set forth above.

9. All other objections and rejections recited in May 15, 2009 are withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642